§440.290c Ticarcillin disodium and clavulanate potassium injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ticarcillin disodium and clavulanate potassium injection is a frozen, aqueous, isoosmotic solution of ticarcillin disodium and clavulanate potassium with one or more suitable and harmless buffer substances. The ratio of ticarcillin to clavulanic acid is 30:1. Each milliliter contains ticarcillin disodium equivalent to 30 milligrams of ticarcillin and clavulanate potassium equivalent to 1 milligram of clavulanic acid. Its ticarcillin content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of ticarcillin that it is represented to contain. Its clavulanate potassium content is satisfactory if it contains not less than 85 percent and not more than 120 percent of the number of milligrams of clavulanic acid that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.5 and not more than 7.5. It passes the identity test. The ticarcillin monosodium monohydrate used conforms to the standards prescribed by §440.91(a)(1). The clavulanate potassium used conforms to the standards prescribed by §455.15(a)(1) of this chapter.

(2) *Labeling.* It shall be labeled in accordance with the requirements of §432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of §431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The ticarcillin monosodium monohydrate used in making the batch for potency, moisture, pH, identity, and crystallinity.

(B) The clavulanate potassium used in making the batch for potency, moisture, pH, identity, and clavam-2-carboxylate content.

(C) The batch for ticarcillin content, clavulanic acid content, sterility, pyrogens, pH, and identity.

(ii) Samples, if required by the Center for Drug Evaluation and Research:

(A) The ticarcillin monosodium monohydrate used in making the batch: 12 packages, each containing approximately 300 milligrams.

(B) The clavulanate potassium used in making the batch: 12 packages, each containing approximately 300 milligrams.

(C) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay.* Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) *Ticarcillin and clavulanic acid contents.* Proceed as directed in §440.290b(b)(1), except use the thawed solution and prepare the sample solution and calculate the ticarcillin and clavulanic acid content as follows:

(i) *Preparation of sample solution.* Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container immediately after thawing and reaching room temperature. Dilute with diluent (described in §440.290b(b)(1)(i)(*c*)) to obtain a solution containing approximately 0.9 milligram of ticarcillin activity per milliliter (estimated). This solution will contain approximately 0.03 milligram of clavulanic acid per milliliter. Introduce the sample into the chromatograph in a timely manner.

(ii) *Calculations.* Calculate the ticarcillin or clavulanic acid concentration as follows:

$$\text{Milligrams of ticarcillin or clavulanic acid activity per milliliter} = \frac{A_u \times P_s \times d}{A_s \times 1{,}000}$$

where:

A_u=Area of the ticarcillin or clavulanic acid peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s=Area of the ticarcillin or clavulanic acid peak in the chromatogram of the ticarcillin or clavulanic acid working standard;

P_s=Ticarcillin or clavulanic acid activity in the ticarcillin-clavulanic acid working standard solution in micrograms per milliliter; and

d=Dilution factor of the sample.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in § 436.20(e)(1).

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 100 milligrams of ticarcillin per kilogram.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

(5) *Identity.* The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the ticarcillin and clavulanic acid working standard.

[55 FR 5840, Feb. 20, 1990]

Subparts D–J [Reserved]

Subpart K—Bulk Drug Formulations for Repacking or for Manufacturing Use

§ 440.1080a Sterile penicillin G potassium buffered.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium, buffered, is a dry mixture of penicillin G potassium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in place of a corresponding amount of sodium citrate. The sodium citrate and citric acid used in making the batch must conform to all U.S.P. specifications. It is so purified and dried that:

(i) Its potency is not less than 1,355 units and not more than 1,595 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH is not less than 6.0 and not more than 8.5.

(vii) Its penicillin G content is not less than 76.3 percent and not more than 89.8 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, loss on drying, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(c) Hydroxylamine colorimetric assay. Proceed as directed in § 436.205 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 20,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.